

The role of prostate size in determining sermic PSA values in patients with benign prostatic hypertrophy

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ABSTRACT

Objective: To determine relationship between prostate volume and serum values of Prostatic Specific Antigen (PSA) among men with Lower Urinary Tract Symptoms (LUTS) caused by Benign Prostatic Hyperplasia (BPH).

Material and Methods: Prospective and retrospective 1420 patients classified in four age-groups with LUTS were analyzed. Patients were treated for BPH in the urology clinical at the University Clinical Center of Kosovo during the period of January 2010-October 2020. Data were recorded from patients according to age, prostate size estimated by transabdominal ultrasound using 3.5MHz ultrasonography, according to the ellipsoid formula, $V = \frac{1}{2} \times D1 \times D2 \times D3 / 2.5$, volume of prostate, $V = \frac{1}{6} \times T \times AP \times CC \times \pi$ where T=Transverse diameter, AP=Antero Posterior diameter, CC=Cranial Caudal diameter. Patients with confirmed prostate cancer were excluded from the study. Statistical analyses used t-test and ANOVA with 95 and 99% confidence intervals.

Results: Mean prostate volume and concentration of serum PSA for the total 142 patients in the study were 46.8 cm³ and 3.5 ng/mL, respectively. It is clear that the both values rises with aging. The mean prostate volume and concentration of serum PSA in the different age- groups respectively were 33.2 cm³ and 1.8 ng/mL (50 years-59 years-old), 37 cm³ and 3.1 ng/mL (60-69 years-old), 49.2 cm³ and 5.1 ng/mL (70 years-79 years-old), and 49.2 cm³ and 5.1 ng/mL (80 years-89 years-old).

Conclusions: The data confirms that prostate volume and PSA concentration of sermic PSA have significant correlation and rises with aging.

Key Words: prostate specific antigen, prostate volume, age, lower urinary tract symptoms

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INTRODUCTION

Benign Prostate Hyperplasia (BPH) is the most common neoplasia appeared in men [1]. BPH probably starts appearing after the age of 30.

On the fourth decade of life the prevalence of pathological signs is only 8%. However, most of males at the age above 50 years old are considered to show LUTS (Lower Urinary Tract Symptoms) which are attributed to BPH.

There is an increase in prostate enlargement in males after the 55th year of life; hence the prevalence of BPH after the 70 years of life is 70% and almost 90% in males after their 80th year of life [1].

Today it's thought that the beginning of the process starts from the transitional area and periurethral glands, on the supramontal zone of the prostatic urethra.

According to Mc Neal (1990) formal genesis of BPH distinguishes: the first phase in which the developed nodules and tissue transition zone on verumontanum are present. The second phase in which under the action of endocrine factors comes to the further development of HBP. The role of age BPH disease is rare before the age of in man.

After the age of 50 the disease appears more often, so at the age of 75 obstructive symptoms are present in around 50% of men and in 30% of men aged 80 prostatectomy interventions is required.

The role of androgen hormones

The presence of testicular androgens and estrogens hormones are necessary in the development of the prostate in the embryo and its intensive growth until puberty. Estrogens have significant action in stroma. They stimulate stromal proliferation and collagen synthesis.

The role of stem cells

Through cell division different types of cells proliferating ability is formed. These cells have limited life period and then follow their programmed death. In old age, there is a blockage in to the maturation process, so the terminal differentiation of cells is locked and thereby decreased death rate of prostate cells is present. Tumor markers could be defined as morphological or biochemical features which inform us regarding the tumor presence, and its proliferative and metastatic potential [1-7]. As tumor markers may serve specific products of tumor benign cells and is also

found in malignant prostate cells - certainly does not represent an ideal tumor marker.

Ideal Tumor markers should be strongly specific and positive only in the presence of prostate cancer and adverse to other diseases.

PSA also is not quite sensitive. This conclusion comes from the fact that 38% to 48% of patients with intra-prostatic carcinoma have normal PSA levels.

If the upper limit of normal PSA serum levels is considered to be 4 ng/mL, as prostate cancer tumor marker compared to BPH has a specificity of 49% and sensitivity of 71%. Despite these shortcomings in clinical practice PSA currently represents the best tumor marker for prostate cancer detection [7].

It is observed that PSA levels increases with age even without cancer existence. The cause of this is the prostate volume growth due to the development of BPH, but to this phenomena contribute the sub-clinical prostatitis, ischemia, infarct of the prostate and "leakage" of PSA which is higher in old age man.

Starting from the 5th decade of life PSA levels rise even in the absence of prostate cancer, its level will increase also in the next decade. Older men have higher PSA values compared to younger males [7].

Dalkin and associates after a study of 5520 men comes to the conclusion that the upper limit of normal values rise after 55 years of life (Table 1) [7].

Today there is a large number of tests for the PSA assessment, among them the most common is the Tandem R, where 100% of healthy people younger than 40 years and 97% of healthy people older than 40 years have PSA values up to 4.0 ng/mL, and none of the examined person older than 40 years does not have the PSA value above 10 ng/mL [8]. Similar to this test there is the tandem E-test, which differs from the previous one in the point where instead of radioactive antibodies, alkaline phosphatase enzyme associated with the antibody is used, even when normal values for this test are 0 ng/mL to 4 ng/mL [7]. ProsChek is a radioimmunoassay using polyclonal antibodies. The PSA upper normal limit using this essay is 2.5 ng/mL. Tests like IRMACount, and the hypersensitive test also should be mentioned, since they are characterized by the minimal detecting activity of PSA up to 0.07 ng/mL. Mentioning newest tests such as Immulite DPD essay of the third generation.

PSA "GRAY AREA"

The gray area represents serum PSA values between 4.1 ng/mL to 10 ng/mL

It is named gray area because PSA increase causes can be different: prostate cancer, HBP, prostatitis, ischemia and prostate infarct as well as various changes caused by age.

To distinguish the causes of high serum PSA levels from prostate cancer, in clinical practice, prostate biopsy is necessary [7].

Study goal

The main goal of the study is: To analyze the correlation between patients age, prostate volume and PSA values in patients with LUTS as a consequence of BPH.

MATERIALS AND METHODS

Prospectively and retrospectively 1420 patients with LUTS (Lower Urinary Tract Symptoms) were analyzed. Patients were treated for BPH in the University Clinical Center of Kosovo-Urology Clinic, during the period of time: January 2010 - October 2020. Data recorded from patients: age, prostate size estimated by transabdominal ultrasound using 3.5 MHz sonde, according to the ellipsoid formula, where $V = D1 \times D2 \times D3 / 2.5$ or Volume of prostate formula = $T \times AP \times CC \times \pi / 6$ where T = Transverse diameter, AP = Antero-Posterior diameter, CC = Cranial Caudal diameter. Also a Digno-Rectal (EDR) examination of prostate was performed. In cases suspected for prostate malignity ultrasound guided biopsy was performed. Patients in which prostate cancer was confirmed were excluded from the study.

PSA values were calculated using IRMA method (Immuno-radiometric Assay) monoclonal antibodies were obtained by a manufacturing company. The manufactured product is IMMUNOTECH - manufacturing company (Czech Republic). Laboratory analysis was conducted at the Institute of Physiology and Immunology in UCCK in Pristina. Determination of PSA levels was based on the use of two different types of mouse monoclonal antibodies. Samples of serum or plasma were placed in test tubes incubated with monoclonal antibodies, which were present in the inner wall of the tube, in the presence of a second monoclonal antibody, which was marked with J125. After incubation the content of the test tube was washed so that antibodies tagged with J125 are left and not connected. Afterwards radioactivity was detected with gamma meters. These values are determined by a standard curve. Total PSA concentration in sample is proportional to the radioactivity. In this research radioactivity was measured by gamma radiation meter type DPC.

The concentration of total PSA in the range of 1420 healthy people is determined by this method. PSA average concentration was 0.77 ng/mL with a standard deviation of 0.76 ng/mL. 95% of the samples had total PSA below 1.8 ng/mL, and 99% of samples below 4.2 ng/mL.

Data is presented through tables and figures. Important statistical parameters were calculated such as the index of structure, the arithmetic average, standard deviation, minimum and maximum values, as well as linear correlation. For data testing t-test was used, and for analysis of variance One Way ANOVA was performed, with a reliability of 95% and 99%, respectively $p < 0.05$ and $p < 0.01$.

RESULTS

The research included 1420 patients with benign prostate hyperplasia.

The average age of the patients involved in the research was 67.33 years old (standard deviation ± 8.07 years). The youngest patient with benign prostate hyperplasia was 50 years old and the oldest 87 years old. Divided by age group, the largest number of patients 67, or 47.2% belonged to the age group 60 years - 69 years old

and 42 patients, or 29.6% to the age group 70 years-79 years old, 21 of them, or 14.8% to the age group 50 years-59 years and 12 patients, or 8.5% of the age group 80-89 years (Table 1 and Figure 1)

Age group	N	%
50 year -59 year	210	14.8
60 year-69 year	670	47.2
70 year-79 year	420	29.6
80 year-89 year	120	8.5
Total	1420	100
Mean \pm SD	67.33 \pm 8.07	
(VJET)		
Range	50 years-87 years	

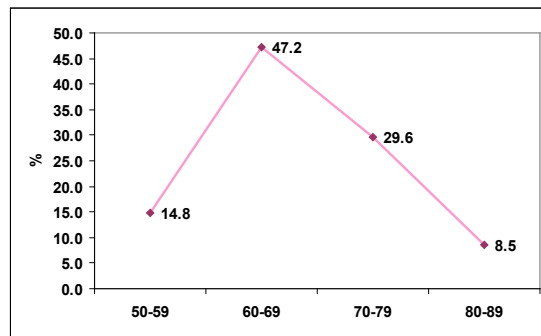


Fig. 1. Structure of patients according to the age group

In Figure 2, we have introduced the degree of correlation between PSA serum concentration in examined persons and prostate volume (cm³). As a result we found a positive

correlation of a medium scale ($r=0.58$, $t=8.32$, $df=140$, $p=0.000$), with the regression line: $y=0.081x - 1.2963$.

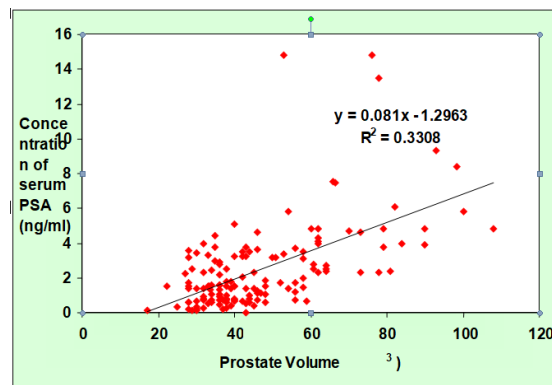


Fig. 2. The correlation between prostate volume (cm³) and PSA serum concentration (ng/mL)

From the regression lines presented, in all cases we expected that without the prostate volume influence - serum PSA concentration should be 1.2963 ng/mL, this concentration increases to 0.081 ng/mL for each cm³ of prostates volume.

In order to measure quantitative changes in serum PSA concentration in examined persons by the influence of prostate volume, from the obtained results we have defined a coefficient of determination with 0.3308 ($R^2=0.3308$), according to which the changes in PSA serum concentration in the examined

persons, in structure of 33.08%, were caused by the impact of prostate volume.

Since $t = t$, df , df , have thrown zero hypothesis (H_0) in a degree of reliability $p=0.01$, in which no significant correlation between serum PSA concentration of examined patients and prostate volume was concluded ($H_0 = 8.32$, $t = 0.01$, $140=2.61$).

In Figure 3 we have introduced the degree of correlation between serum PSA concentrations of examined persons and age (years). We found a positive correlation, of a low scale ($r=0.33$, $t=4.19$, $df=140$, $p=0.000$), with the regression line: $y=0.1093x - 3.9207$. From the regression lines presented, we see that in all cases, without age impact - serum PSA concentration to be 3.9207 ng/mL. This concentration increased to 0.1093 ng/mL per year.

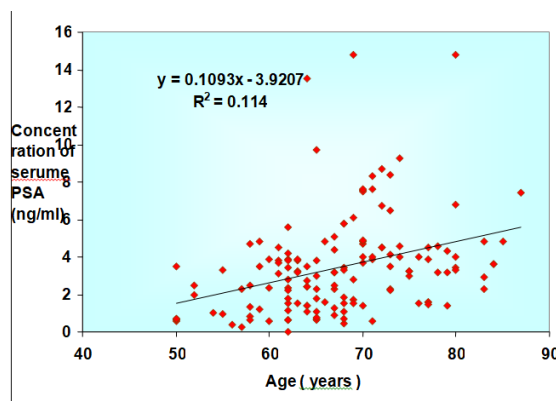


Fig. 3. The correlation between serum PSA concentration (ng/mL) and age (years)

In order to measure quantitative changes in serum PSA concentration of examined persons by the influence of age from the obtained results we have defined a coefficient of determination of 0114 ($R^2=0,114$), according to which the concentration of PSA changes in the serum of the examined persons, in the structure of 11.4%, were caused by the influence of age.

Since $t = t(2)$, df , we have thrown zero hypothesis (H_0) in degree of reliability $p=0.01$, according to which there is no

significant correlation between serum PSA concentration of examined persons and their age ($H_0 = 4.19$, $t = 0.01(2)$, $140=2.61$).

In our clinical material, most patients - 1030 of them or 72.5% had serum PSA concentration below 4.1 ng/mL, 360 or 25.4% of 4.1 ng/mL-10 ng/mL i.e. belong gray area (Table 2 and Figure 4).

Tab. 1. Patients according to the concentration of PSA values

PSA values	N	%
<4.1 ng/mL	1030	72.5
4.1 ng/mL-10 ng/mL	360	25.4
>10 ng/mL	30	2.1
Total	1420	100

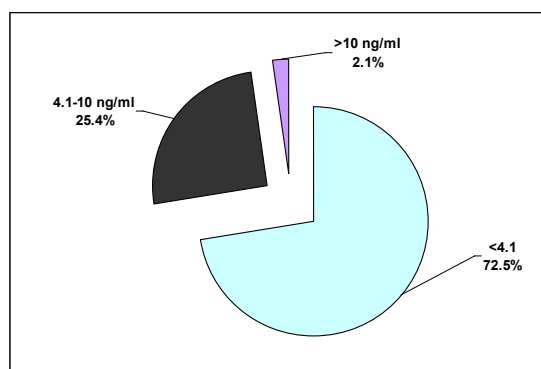


Fig. 4. Structure of patients belonging to the "gray zone"

Table 3 Presents the average prostate volume of gray zone patients and patients with PSA concentration <4.1 ng/mL. The average prostate volume for gray zone patients was 44.6 cm³ (Standard Deviation ± 11.6 cm³), while the average prostate

volume patients with PSA values <4.1ng/mL is 36.9 cm³ (Standard Deviation ± 8.2 cm³). T-test obtained a distinction with a high statistical significance between prostate volume of the two groups (t=4.328, p<0.0001).

PSA Values	Volume of prostate cm ³		T-test
	Mean	SD	p-value
<4.1 ng/mL n=1030	36.9	8.2	t=4.328 p<0.0001
4.1 ng/mL-10 ng/mL n=360	44.6	11.6	

Using multiple correlation a positive correlation of medium scale (r=0,426) between age, prostate volume and serum PSA values

was gained I.e. by aging- prostate volume and serum PSA values increase (Table 4 and Figure 5) .

Age -group	N	%	Volume of prostate (cm ³)	PSA
				(ng/mL)
50 year -59 year	210	14.8	33.2	1.8
60 year -69 year	670	47.2	37	3.1
70 year -79 year	420	29.6	43	4.4
80 year -89 year	120	8.5	49.2	5.1
Total	1420	100	46.8	3.5

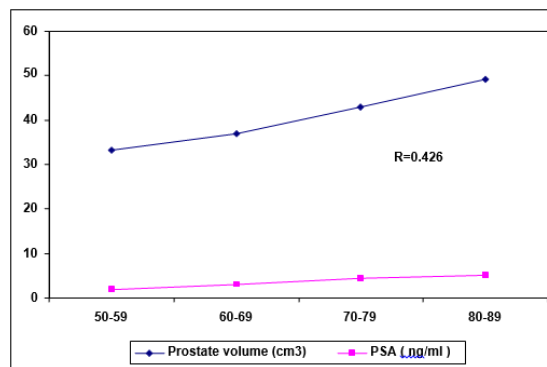


Fig. 5. Correlation between age, prostate volume and PSA levels

DISCUSSION

Despite the fact that PSA today is considered the leading tumor marker in prostate cancer detection, it is still far away as being an ideal tumor marker. Ideal tumor markers should be strongly specific to prostate cancer and negative to other diseases. PSA does not fulfill this condition [1, 7-11].

PSA also is not very sensitive, from the fact that 38% to 48% of patients with intra-prostatic cancer have normal PSA values.

Despite these shortcomings PSA is still considered the main tumor marker tool in prostate carcinoma detection [7, 9, 11].

PSA is strongly correlated with prostate volume and age in patients with BPH. It is proved that at the age of 60, the incidence of BPH is around 60%, whereas in the eighth decade approximately in 95.5% of men BPH is present [7-11].

According to Pervorfi in 80 years old males' microscopical changes belonging to BPH were found in almost all cases, despite patients' race, nationality or religious background [6].

Having in consideration that high BPH incidence is associated with prostate volume enlargement and in a strong correlation with increased values of serum PSA; therefore as a conclusion PSA shows an important role in diagnose and treatment of BPH patients [1-26].

Prostate volume and PSA both represent an age dependent variables. Histological normal prostate tissue reaches a weight of 20 g in males aged 21-30 years and this weight remains constant until the start of BPH development [27-36]. In a normal population prostate weight grows with the increase of the age, this phenomena was observed during autopsies. The prostate weight or volume in patients with LUTS (Low Urinary Tract Symptoms) is greater than in normal population [1]. Serum PSA in our study had significant correlation with prostate volume. Hence the greater the prostate volume, there is a greater risk for AUR (Acute Urinary Retention) and an indication for surgery [1, 4]. Serum PSA is important in calculating prostate volume enlargement and also in determining individual treatment of HBP [2]. Previously it was noted that PSA and PV (Prostate Volume) in patients with BPH increase with age. The ability to use serum PSA to predict prostate volume can be very useful in the treatment of patients with HBP. This phenomena is very useful especially for patients with BPH with prostate volume above 40ml, in that case 5 α reductase inhibitors such as finasterid is more effective in patients with prostate volume >40 mL and sPSA >1.5 ng/mL [2]. This suggests that there is a limit of prostate gland size higher than 40 ml so the symptoms of BPH could appear. Increased serum PSA values except BPH and prostate cancer, also affects many other factors such as urethral catheterization, acute prostate inflammation, AUR (Acute Urinary Retention), then endo-urologic interventions such as cystoscopy, Prostate TUR, and prostate biopsy etc [4]. A correlation between AUR and PSA was determined in patients with chronic prostate inflammation [4]. PSA level above 4 ng/mL were detected in 64% of AUR patients and 38% in patients without AUR. Mean PSA levels in patients with chronic prostate inflammation in AUR was 7.75 ng/mL while in patients without AUR was 5.32 ng/mL [4]. Nadler and Co. also referred that prostate chronic inflammation increased PSA levels and these data were more compatible with other author's results such as Iran and co. which has also demonstrated that inflammation in the prostate biopsy has significantly increased PSA levels as a result of damaged glandular epithelium [4]. Damage to the integrity of the prostate gland from inflammation may be the main cause of increased PSA values in the group with AUR (Acute Urinary Retention). Every pathology that damages the prostate glands leads to distribution of prostate intraluminal secretion through stromal vascular structures and thus increases serum PSA levels. For the particular reason we suggest that prostate chronic inflammation seems to play a very important role in patients with AUR as result of BPH and consequently increases PSA serum levels [4]. Through our research we have established a significant correlation between two important parameters such as prostate volume and serum PSA values.

Statistics of prostate main volume (prostate volume classification according to Lege) and corresponding PSA serum levels for 142 patients with LUTS due to BPH are reflected in Figure 5.

In Figure 5 the degree of correlation between serum PSA concentration and prostate volume (cm³) in examined patients is presented. A positive correlation, of a medium scale was obtained ($r=0.58$, $t=8.32$, $df=140$, $p=0.000$), with the regression line: $y=0.081x - 1.2963$.

From the regression lines presented, we see that in all cases without the prostate volume influence, PSA serum concentration is 1.2963 ng/mL, this concentration increases to 0.081 ng/mL for each cm³ of prostates volume.

On the other side prostate size examination and serum PSA values corresponded to patients with HBP classified by age group where through multiple correlation a positive correlation of a medium scale was obtained ($r=0,426$) between age, prostate volume and PSA values in the serum of researched patients. I.e. by aging prostate volume and serum PSA values increase.

These results match with the results of other authors eg. Stepan V. and co-authors Department of Urology, University Hospital -Goteborg Sweden which studied the correlation between prostate volume and serum PSA concentration in 354 males with LUTS (Lower Urinary Tract Symptoms) as a result of BPH [1-3, 11-14, 18-21, 36-45]. In their study the prostate average volume was 40.1 cm³, and the average concentration of serum PSA was 3.99 ng/mL. These values match with our values, in which average prostate volume was 46.8cm³ and average value of the corresponding serum PSA was 3.5 ng/mL [1].

Even in our study as well as in other authors' studies it is noted that prostate volume as well as serum PSA are parameters that increase with age.

On the other hand given the correlation between prostate volume and serum PSA value, depending on PSA values prostate size can be predicted [2].

We have also analyzed the degree of correlation between serum PSA concentrations of examined patients and age (years). A positive correlation of a low scale was obtained ($r=0:33$, $t=4.19$, $DF=140$, $p=0.000$), with the regression line: $y=0.1093x - 3.9207$. These results match well with the results of other author's studies [1-3, 7, 11-21, 36-40]. So, it can be concluded that with increasing age of patients suffering from BPH, PSA serum levels increase.

On the other hand, Dalkin and co. (1993) after a study of 5520 men comes to a conclusion that the upper limit of normal values increases after 55 years of life.

Serum PSA values upper limit

- 4.0 ng/mL - 55 years to 59 years old
- 5.4 ng/mL - 60 years to 64 years old
- 6.2 ng/mL - 65 years to 69 years old
- 6.6 ng/mL - 70 years to 74 years old

The most important cause of PSA growth in relation to age is prostate volume enlargement due to BPH. This phenomenon is

also helped by factors such as sub-clinical prostatitis, ischemia and prostate infarct, occult cancer.

According to many authors the correlation between PSA and age is statistically significant [7, 11].

The analysis of age and prostate volume (cm^3) correlation concludes a positive correlation, of a low scale ($r=0.39$, $t=4.99$, $df=140$, $p=0.000$).

Our results show that increased patients age causes prostate volume growth. Our results approximately match with those of other authors so, according to a study at the University Hospital of Gothenburg in Sweden with patients aged <54 years corresponds to the average prostate volume of 27.53 cm^3 , age group 55 years-59 years responds average prostate volume of 28.76 cm^3 , aged group 60 years -64 years and 65 years -69 years responds average prostate volume of 34.93 cm^3 and 39.33 cm^3 , aged group 70 years-74 years and 75 years-79 years corresponds to the average prostate volume of 43.6 cm^3 and 40.54 cm^3 , and age group >80 years corresponds to the average prostate volume of 48.24 cm^3 . From the presented data it is clear that age increases the average prostate volume [1-21, 36-39].

According to our results the age group challenged by increased average prostate volume as a result of HBP was 60 years-69 years old with 47.2% of patients who had prostate average volume of 37.0 cm^3 .

According to Markovic (2000) BPH disease appears rare before the age of 50, and after this age the disease is more frequent so that around 50% of men have symptoms of obstructive prostatism. 20%-30% of men aged 80 years need a prostatectomy [11].

Summary statistics regarding the average prostate volume and PSA in 142 males with LUTS due to BPH show that average prostate volume was 46.8 cm^3 and average PSA concentration was 3.5 ng/mL . It is clear that both values increase with age. So, in the age group 50 years - 59 years average prostate volume and PSA average was 33.2 cm^3 and the concentration of serum PSA was 1.8 ng/mL . These values increase progressively so that the age group of 60 years-69 years patients have prostate average volume of 37 cm^3 and PSA 3.1 ng/ml , the age group 70 years-79 years is the average volume of 43.0 cm^3 and PSA 4.4 ng/ml , the

age group of 80 years-89 years have prostate average volume of 49.2 cm^3 and PSA of 5.1 ng/mL . Our results nearly match those of other authors [1-14, 18-21, 36-40].

Using a Multiple correlation between patients age, prostate volume and PSA serum levels a positive correlation of a middle scale was obtained ($r=0.426$) i.e. by aging prostate volume and PSA levels increase.

In Gray zone patients' average prostate volume was 44.6 cm^3 , and the average value of serum PSA was 5.9 ng/mL . As we can see both values rise with aging. So, the average prostate volume of 40.5 cm^3 and average serum PSA of 4.8 ng/mL responds to patients aged 50 years-59 years, these values increase progressively, so that in the age group of 80 years-89 years average prostate volume was 51.3 cm^3 and PSA serum values of 7.2 ng/mL .

In "gray zone" patients using the MULTIPLE correlation a positive correlation of a low level ($r=0.293$) was gained, comparing patients age, prostate volume and serum PSA.

According to a study by Aykut Kefi with coll. of the Department of Urology at Dokuz Eylul University in Turkey PSA values increase with age, also in other conditions such as: carcinoma of the prostate, urethral catheterizing, acute prostatitis, etc RAU [4].

According to Markovic 2007 "gray zone" represents PSA values between 4.1 ng/mL to 10 ng/mL . It is called 'grey zone' because the causes of rising PSA may be different as prostate cancer, BPH, prostatitis, ischemia of prostate, prostate cancer and various changes caused by age [7, 11].

To distinguish these causes of increasing the value of serum PSA from prostate cancer in clinical practice, prostate biopsy is necessary [7].

CONCLUSION

Corresponding values of prostate volume and corresponding serum PSA increase with increasing age of patients with BPH.

FUNDING

None

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